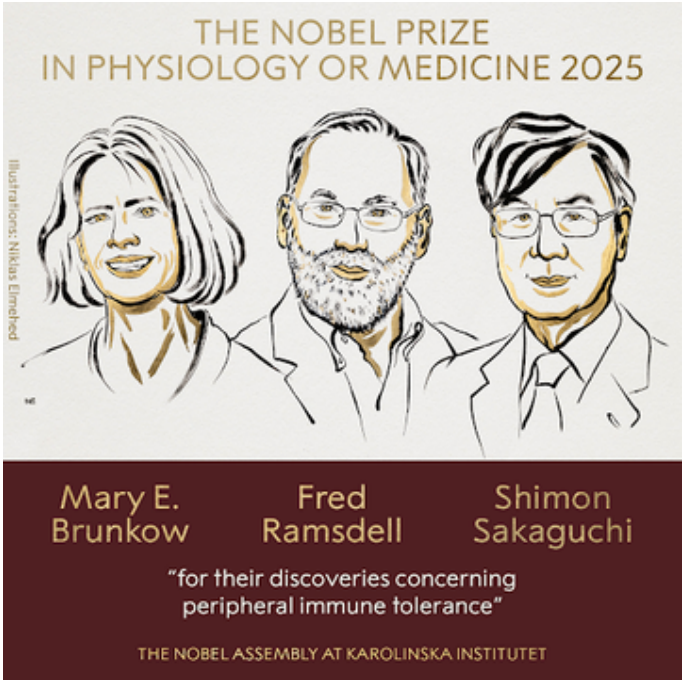
# Nobel Prizes in Science 2025 : An Appreciation

S T Lakshmikumar

This is an attempt to appreciate the science which has been recognized and rewarded with Nobel prizes in Chemistry, Physics and Medicine for the year 2025, an annual effort on my part for the past many years.




We begin with the Nobel Prize in Physiology or Medicine (2025) which was awarded to Mary E. Brunkow, Fred Ramsdell, and Shimon Sakaguchi *"for their discoveries concerning peripheral immune tolerance"*. Immunity is as important a part of Darwinian evolution as reproduction. The struggle between a pathogen and host is in a way a fight between predator and prey. Immunity is what guards the largest living organism, the blue whale, from the smallest "living" organism, a virus. Advances in immunology have been crucial for reduced human mortality. Not very surprisingly many advances in immunology were recognised with Nobel prizes in physiology or medicine. As early as 1880 Paul Ehrlich (Nobel Prize in Medicine 1908) microscopically identified the different types of white blood cells which are the key contributors to immunity and developed a chemical structure theory to explain immune response. This "side chain theory" mentions molecules and side chains but this was an era when atoms and molecules were inferred rather than observed. Ehrlich's theory was a logical exploration of the germ theory of disease which Louis Pasteur had established a few decades earlier. It formed the basis for understanding innate and adaptive immunity. Innate immunity is non-specific and present from birth while adaptive or acquired immunity is a slower but highly specific response that learns from infections, creating a memory of past infection for long-lasting protection. Inflammation and fever are responses of innate immunity. As Ehrlich reasoned, this would mean that molecules that detected germs and distinguished them from cells of the host exist in the body. In 1957 Frank Burnet (Nobel prize in medicine 1960) provided a molecule level description of adoptive immunity with the clonal selection theory. With the development of modern molecular biology it has become possible to study most of the steps of clonal selection at the molecular level. But Burnet just like Ehrlich argued from organism level observations.

We now know that the first step in innate immunity is the detection of pathogens by cells such as macrophages which have toll-like receptors on their surface. These receptors detect the difference in the shapes of surface protein molecules of the host and pathogens. The second step is dilation of blood vessels (inflammation) and release of generic chemical agents poisonous to most pathogens. Fever, an increase in body temperature is another attempt to kill pathogens. The toll-like receptors trigger these changes.

A third step is the macrophage breaking down the pathogen and presenting its fragments called antigens on special molecules. Adaptive immunity now takes over. The antigens activate T-helper cells (with a CD4 protein on the surface) whose numbers increase rapidly. Simultaneously numbers of B-cells that recognize free antigens increase which activates more T cells. The B cells mutate randomly. Mutants whose protein structure better matches the antigen surface have a much faster increase in numbers. Thus, the affinity to the antigens is maximized. This is followed by cloning of a large number of B cells with maximum affinity. Clonal expansion of B cells is followed by creation of plasma cells which create a massive number of antibodies specific to the antigen. Then memory cells are created which increase the speed of response to future attacks by the same pathogen. Finally cytotoxic or killer T-cells (with a CD8+ protein on the surface) are created to kill infected cells.

Brunkow, Ramsdell and Sakaguchi have uncovered an additional pathway in this already complex immunological response. The discovery is extremely fascinating as it highlights the innate complexity of living organisms. One should remember that even a unicellular organism has several thousand feedback loops according to most estimates.

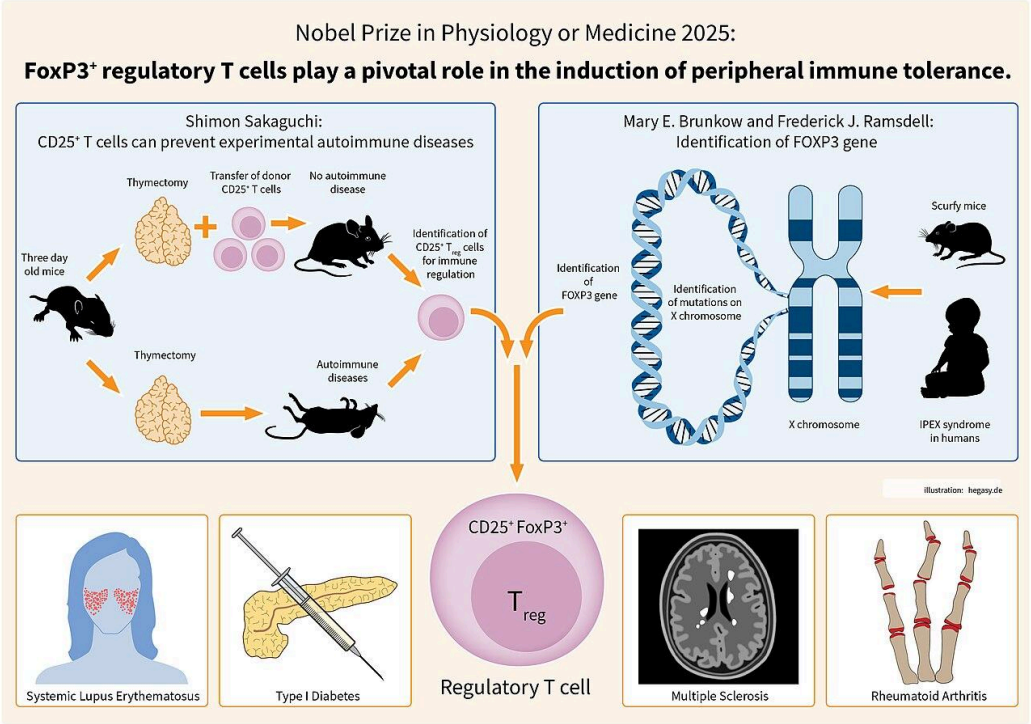
Ehrlich and Burnet highlighted a crucial issue that has also been discussed by other scientists too. The immune system targets both external pathogens and infected cells in the organism. How do the helper T-cells avoid attacking the healthy cells in the organism? Why are T-helper(CD4) cells that attack healthy cells in the organism not produced during random mutation? There obviously must have been a mechanism to restrain T cells that attack healthy cells since there are autoimmune diseases. Failure of the restrain mechanism is the obvious cause of such diseases. It was soon discovered that the Thymus helps eliminate any T cells that could potentially target the healthy cells. This is called central tolerance. Just like most biological processes, the elimination of self attacking T-cells in the Thymus is not fool proof. Many scientists wondered if there were other pathways for improving central tolerance just as there are error correction mechanisms for other biological processes. But the details of any such restraining mechanism were elusive.

Sakaguchi was inspired by an earlier experiment where the Thymus of mice was surgically removed three days after birth. It was expected that the mice will have very weak immunity. But the mice developed autoimmune disease. Sakaguchi isolated T cells that had matured in genetically identical mice and injected them into the mice without a thymus. This protected the mice from autoimmune diseases. Normally the helper T-cells(CD4) used by Sakaguchi, should only have increased the immune response but in this experiment, the immune response was constrained leading to the reversal of autoimmune diseases. Sakaguchi concluded that there must be two different types of helper T-cells carrying the CD4+ protein. After ten years of effort, he could show that there is a sub class of helper T-cells carrying CD25+ protein in addition to CD4 and that only these cells could reverse the autoimmune diseases in the experiments. He labelled them regulatory T cells or Treg cells. However, the scientific community was skeptical. The work of Brunkow and Ramsdell provided the evidence that overcame the scepticism.

Just like Sakaguchi, Brunkow and Ramsdell started with an earlier largely unnoticed result. The effect of radiation on mice was studied originally as part of the Manhattan Project (for development of the atomic bomb). A new strain of mice called “scurfy” was observed after exposing the mice to radiation. Some male “scurfy” mice were unexpectedly born with scaly and flaky skin, an extremely enlarged

spleen and enlarged lymph glands. These “scurfy” mice lived for just a few weeks. The females and fifty percent of males however did not exhibit the “scurfy” symptoms even though this mutation was present showing that the mutant gene was on the X chromosome. The male mice are susceptible to severe disease because the organs are being attacked by T cells. The immune system is obviously out of control.

Brunkow and Ramsdell decided to identify the genetic mutation responsible for the “scurfy” mice strain. Techniques for rapid mapping of genomes and comparing them had not yet been developed. So Brunkow and Ramsdell had to work laboriously for several years to identify the mutant gene responsible for the “scurfy” mice. They labelled it Foxp3. They also suspected that an extremely rare autoimmune disease in children called IPEX was a human equivalent of Foxp3. They collected DNA samples from pediatricians treating these children all over the world and proved that this conjecture was true. Two years after these results were published, Sakaguchi conclusively proved that Foxp3 controls the development of regulatory T-cells. The Treg cells prevent other T-cells from mistakenly attacking the body's own healthy tissue. Treg cells also reduce the T-cell activity after an infection triggering them has been overcome.

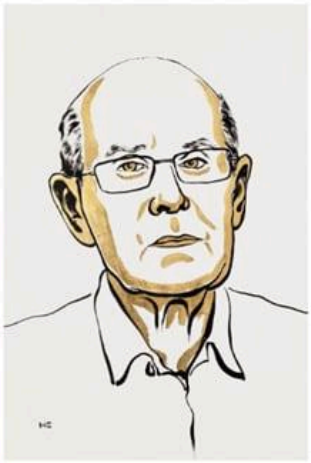

Nobel Prize in Physiology or Medicine 2025:
FoxP3⁺ regulatory T cells play a pivotal role in the induction of peripheral immune tolerance.
Shimon Sakaguchi:
CD25⁺ T cells can prevent experimental autoimmune diseases
Thymectomy
Transfer of donor CD25⁺ T cells
No autoimmune disease
Three day old mice
Identification of CD25⁺ Treg cells for immune regulation
Thymectomy
Autoimmune diseases
Mary E. Brunkow and Frederick J. Ramsdell:
Identification of FOXP3 gene
Scurfy mice
Identification of FOXP3 gene
Identification of mutations on X chromosome
X chromosome
IPEX syndrome in humans
illustration: hegasy.de
CD25⁺ FoxP3⁺
Treg
Regulatory T cell
Systemic Lupus Erythematosus
Type I Diabetes
Multiple Sclerosis
Rheumatoid Arthritis

The scientific knowledge discovered by Brunkow, Ramsdell and Sakaguchi summarized in the picture above is becoming the basis for several new medical treatments. A large number of people suffer from rheumatoid arthritis, type 1 diabetes, multiple sclerosis, and lupus which are all autoimmune diseases. Researchers are trying to increase the availability of Treg cells by giving patients *interleukin-2*, a substance that makes regulatory T cells thrive. A similar approach is being investigated to prevent organ rejection after transplantation. Cloning of Treg cells of the patients is another approach which is being explored as a treatment for autoimmune diseases. Attaching antibodies to the cloned cells may help protect transplanted organs. Tumors attract regulatory T cells. Dismantling this protection could enable the immune system to attack the tumors. Curiously, the 2018 Nobel Prize in Physiology or Medicine was awarded to James Allison and Tasuku Honjo for the discovery of a new cancer therapy that works by inhibiting negative immune regulation. They identified proteins (like CTLA-4 and PD-1) that act as "brakes" on the immune system's T cells which allows T-cells to attack cancer. The 2018 and 2025 awards are for complimentary approaches to controlling immune regulation, for treating different diseases.

Ill. Niklas Elmehed © Nobel Prize Outreach

Susumu Kitagawa

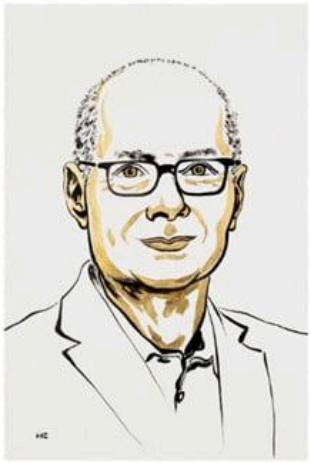
Prize share: 1/3



Ill. Niklas Elmehed © Nobel Prize Outreach

Richard Robson

Prize share: 1/3

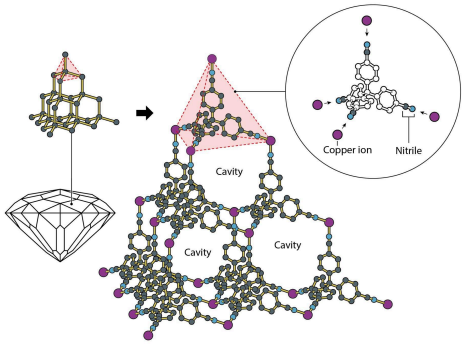


Ill. Niklas Elmehed © Nobel Prize Outreach

Omar M. Yaghi

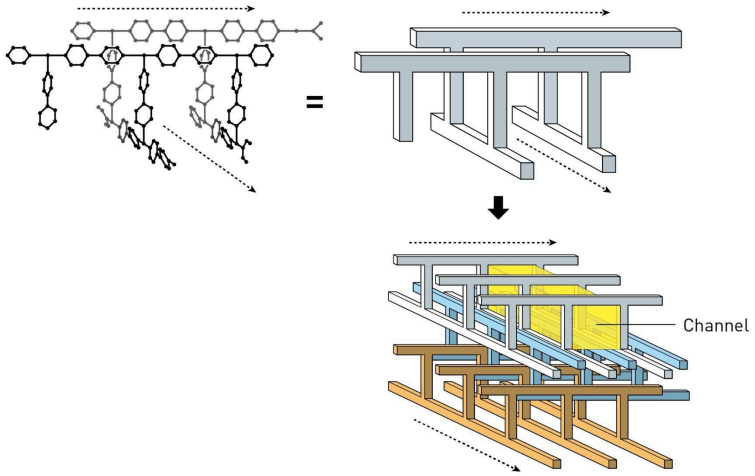
Prize share: 1/3

The Nobel prize in Chemistry (2025) was awarded to Susumu Kitagawa, Richard Robson and Omar M. Yaghi *"for the development of metal–organic frameworks".* This cryptic statement does little to reveal the uniqueness of the work. Quite apart from leading to many revolutionary technological applications in the near future, metal-organic frameworks are a paradigm shift in the chemists' repertoire. Even earlier to the work of the laureates, skilled experimentalists could construct almost any complex molecule imaginable. The nature of the chemical bond between any two elements is completely understood. However, all this does not help a chemist to predict in what way a large number of atoms or molecules would organise themselves. We know that diamond is pure carbon as are graphite and activated charcoal. But the three have completely different chemical properties because the arrangement of carbon atoms in each is totally different. This is hardly unique. Small differences in temperature, pressure or atomic radius may lead to completely different arrangements of atoms but these cannot be calculated from theory. The laureates have shown how to assemble small building blocks into the metal organic framework with a predetermined arrangement. Further, they have created two phase materials with the second chemical constituent loosely bound to the metal organic framework. They have opened a path to the creation of frameworks with a wide range of different pieces of different shapes and characters, thus creating a potential for the rational design of MOFs for different applications.

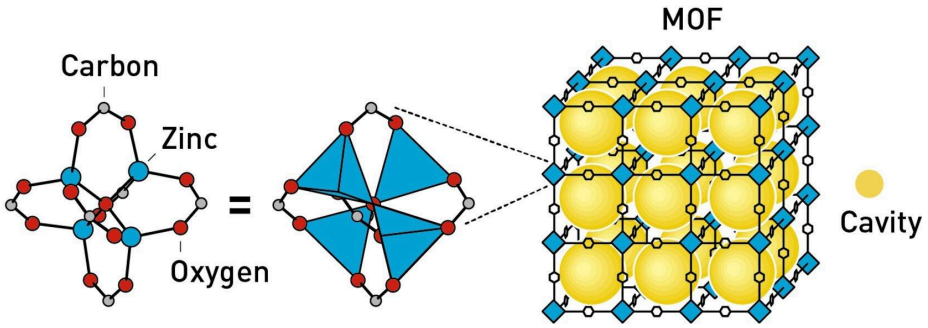


In his quest to build extended three dimensional molecular structures using suitable building blocks, Robson chose to employ a relatively rigid tetranitrile (4',4″,4‴,4⁗ - tetracyanotetraphenylmethane) and a copper ion, both with tetrahedral symmetry. His goal was to build an extended diamond-like structure as shown in the figure above. His choices were influenced by earlier research, such as the development of the Hofmann clathrate and perhaps the determination of the structure of Prussian blue pigment in the first half of the twentieth century. The Hofmann clathrate consists of extended sheets of nickel cyanide coordination entities between which molecules of benzene were trapped. The Prussian blue pigment consists of repeated $–Fe^{II}–CN–Fe^{III}–$ sequences, forming a three-dimensional cubic framework inside which water molecules and cyanide ions are trapped. Robson confirmed the formation of an extended three dimensional diamond like three dimensional framework with relatively large cavities. Robson predicted and to some extent demonstrated the properties of such networks. He foresaw that diffusion of molecular or ionic species could take place throughout the cavities in these structures leading to application as molecular sieves or for ion-exchange. He predicted structures with improved stability, modification of the frameworks after the formation, development of frameworks that could withstand vacuum treatment to remove inclusions and integrating catalytic sites into the framework.

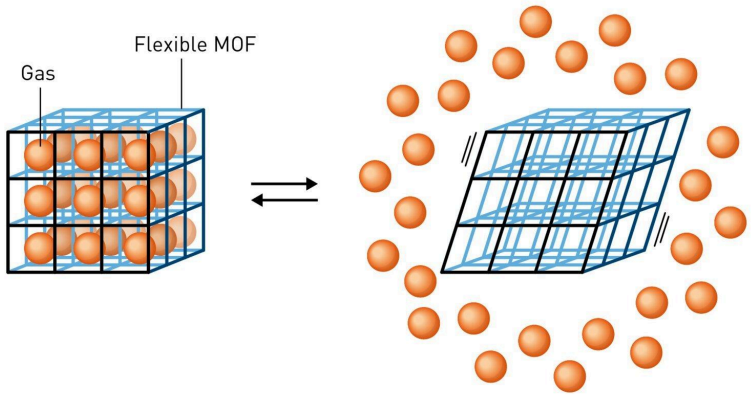
Kitagawa and Yaghi made significant contributions in the efforts made for the practical realisation of the potential of metal organic frameworks that was indicated by Robson's work. They developed more robust frameworks that have led to practicable technology. One of the first significant steps was Yaghi's demonstration of MOFs stable upto 350C. One significant result due to Kitagawa and coworkers was the "tongue and groove" framework which was used to demonstrate adsorption and desorption of gases like methane oxygen and nitrogen at room temperature.



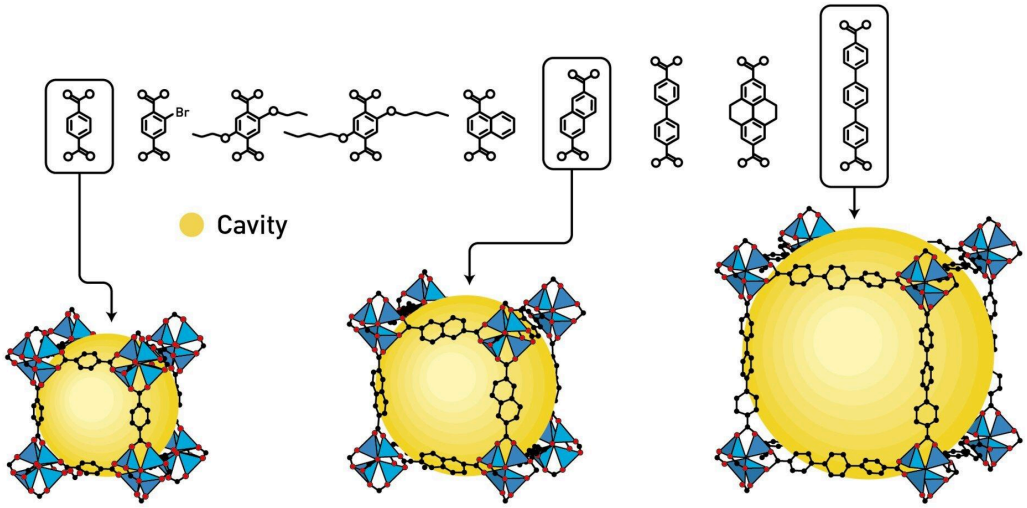

In this geometry protruding ridges (tongues) fit into adjacent grooves within the material. Since zeolites were well established for gas adsorption however, the response to Kitagawa's results was lukewarm. In 1999, Yaghi and coworkers, by choosing conditions that led to the formation of $Zn_4O$-carboxylate clusters as secondary building units (SBUs) produced a highly stable framework - MOF-5.



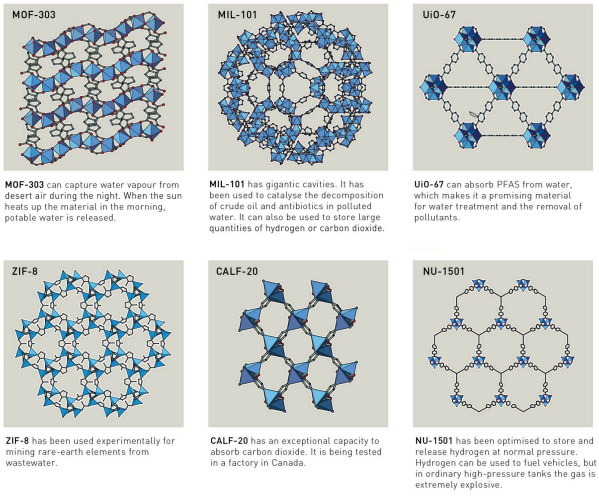

The MOF-5 structure shown above has permanent porosity, with the crystal structure intact upon evacuation of guest molecules, and high thermal stability. A Langmuir surface area of 2900 $m^2/g$ could also be estimated (using $N_2$), and an associated pore volume of approximately 0.6 $cm^3/mL$. For comparison, zeolites have typical surface areas of several hundred square meters per gram, while activated carbon materials can reach somewhat higher values. These values demonstrated that the frameworks had properties similar to commonly used, commercial sorbents, which resulted in increased interest from industry. Because of the relatively long organic chains, MOFs are flexible. Kitagawa introduced the notion of three “generations” of frameworks, where the first generation represents porous structures that are unstable upon removal of the inclusions; the second generation being  frameworks capable of reversibly releasing and readsorbing guest species while maintaining their phase and morphology and finally a third generation that can change their morphology in response to external stimuli (pressure, temperature, light, etc.). He subsequently demonstrated that his tongue and groove framework was a third generation framework.The adsorbed gases could be desorbed by flexing the material as schematically shown below



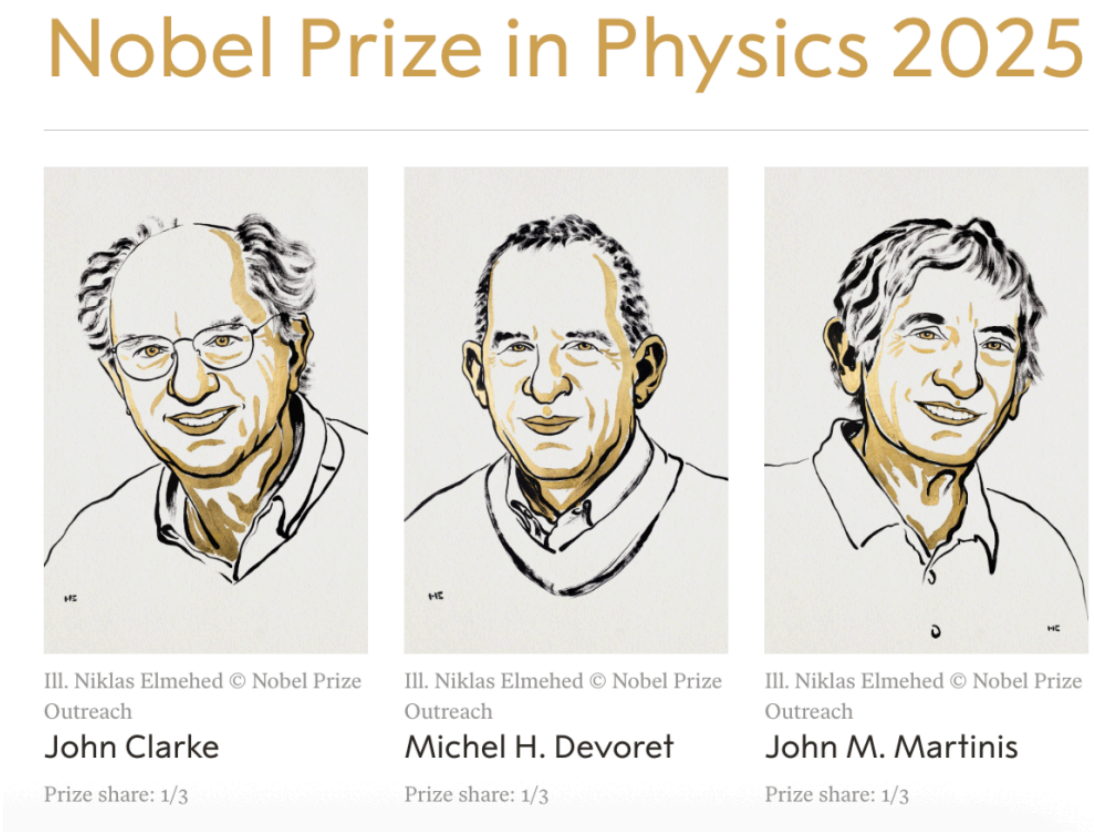
Yaghi developed a series of  frameworks with different cavity sizes and linker functionalities by using the same SBU but varying the organic linker unit as shown below




Gas adsorption is dependent on the porosity of the material.  Intense efforts were also made to develop frameworks with high surface areas and pore sizes. For example, the MOF-177 framework displayed a Langmuir surface area of 4500 m²/g. MOF-210 showed values of >10,000 m²/g (Langmuir). A similar high surface area was recorded for framework NU-100. This structure showed high storage capacities for hydrogen (164 mg/g) and carbon dioxide (2315 mg/g). IRMOF-16 is a mesoporous framework with pore sizes of 2.8 nm.  Very large pores (apertures of up to 9.8 nm) were reported for the frame-work IRMOF-74-XI. These numbers are attractive for commercial use and major industries are investing heavily to bring them into the market. So far they have only been demonstrated at a small scale but many scientists think that metal organic frameworks as materials will dominate the twenty first century. Some of the significant demonstrations are shown in the picture below.

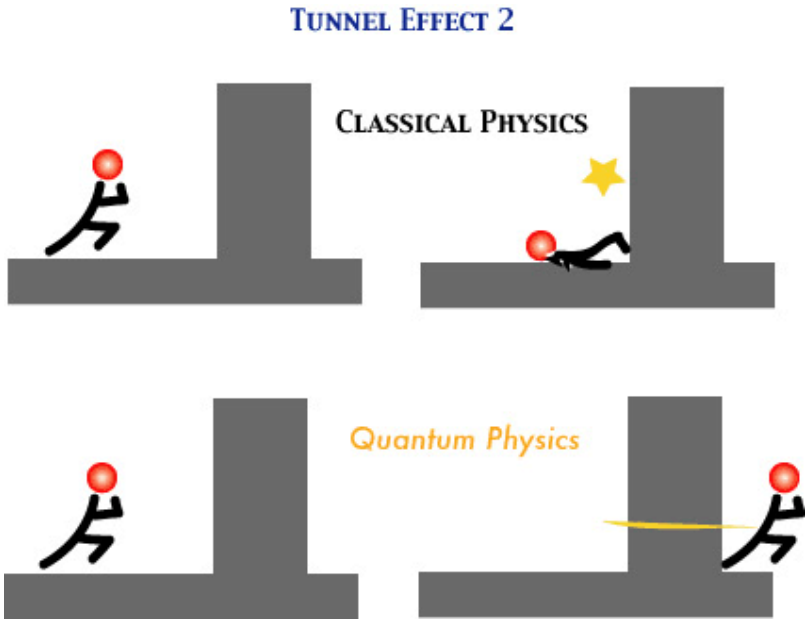

MOF-303
MOF-303 can capture water vapour from desert air during the night. When the sun heats up the material in the morning, potable water is released.
MIL-101
MIL-101 has gigantic cavities. It has been used to catalyse the decomposition of crude oil and antibiotics in polluted water. It can also be used to store large quantities of hydrogen or carbon dioxide.
UiO-67
UiO-67 can absorb PFAS from water, which makes it a promising material for water treatment and the removal of pollutants.
ZIF-8
ZIF-8 has been used experimentally for mining rare-earth elements from wastewater.
CALF-20
CALF-20 has an exceptional capacity to absorb carbon dioxide. It is being tested in a factory in Canada.
NU-1501
NU-1501 has been optimised to store and release hydrogen at normal pressure. Hydrogen can be used to fuel vehicles, but in ordinary high-pressure tanks the gas is extremely explosive.

MOF-303 captures water vapour from desert air during the night. When the sun heats up the material in the morning, potable water is released. MIL-101 has gigantic cavities. It has been used to catalyse the decomposition of crude oil and antibiotics in polluted water. It can also be used to store large quantities of hydrogen or carbon dioxide. UiO-67 can absorb PFAS from water, which makes it a promising material for water treatment and the removal of pollutants. ZIF-8 has been used experimentally for mining rare-earth elements from wastewater. CALF-20 has an exceptional capacity to absorb carbon dioxide. It is being tested in a factory in Canada. NU-1501 has been optimised to store and release hydrogen at normal pressure. So far, hydrogen could not be used to fuel commercial vehicles because ordinary high-pressure hydrogen tanks carry a risk of explosions. The semiconductor industry is already using MOFs for storing the highly toxic gases needed in the silicon foundry. At the other end new concepts are being explored in research laboratories. Examples include framework thin films on surfaces, surface-modified frameworks, hybridised frameworks and core-shell structures. Some others are more exotic such as modulating the coordination to control framework extension, forming disordered “glassy” frameworks, polymerization within the frameworks and frameworks that are proton conductors.


Nobel Prize in Physics 2025
Ill. Niklas Elmehed © Nobel Prize Outreach
John Clarke
Prize share: 1/3
Ill. Niklas Elmehed © Nobel Prize Outreach
Michel H. Devoret
Prize share: 1/3
Ill. Niklas Elmehed © Nobel Prize Outreach
John M. Martinis
Prize share: 1/3

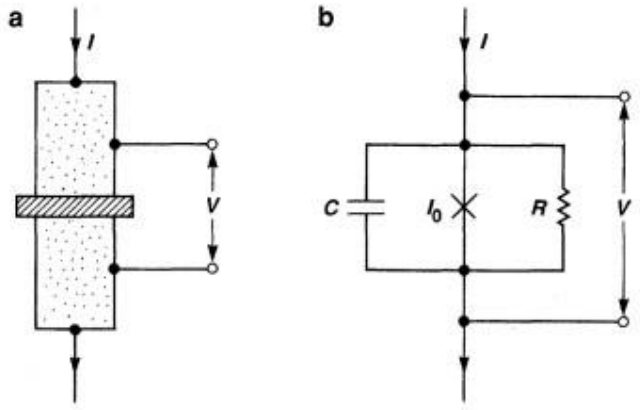
The Nobel Prize in Physics 2025 was awarded to John Clarke, Michel H. Devoret and John M. Martinis *“for the discovery of macroscopic quantum mechanical tunnelling and energy quantisation in an electric circuit.”* The citation does not even mention that the electric circuit employed is a superconducting Josephson junction. But superconductivity and Josephson tunneling are crucial to the “electrical circuit” used in the study. Superconductivity was discovered by Kamelingh Onnes in 1911. The resistance of a macroscopic superconductor is exactly zero. A current that flows in superconducting ring is theoretically predicted not to decrease in 13.8 billion years, the best estimate for the age of the universe. And the superconducting ring is a real material with defects and impurities which change their normal state resistance but apparently do not contribute to the zero resistance of a superconductor. This mystery was explained by the microscopic theory of superconductivity developed by Bardeen, Cooper and Schrieffer (Nobel Prize in Physics 1972). This theory explains that

below a particular temperature, the electrons in the superconducting material couple in pairs to form a composite boson called a Cooper pair. Like all bosons they do not interact with each other. The best example is two light beams that can cross each other without interfering with each other. Light consists of bosons called photons. A laser beam is a special type of light beam whose diameter does not increase. Hence it is possible to use a laser pointer. Just as all the bosons in the laser beam are "coherent" and exhibit interesting properties, all the Cooper pairs in a superconductor settle into a single state and exhibit superconductivity. The electrons in a superconductor form a macroscopic state. Josephson considered a special situation where two macroscopic superconductors are separated by a thin insulator, called a Josephson junction. He showed that superconducting current will tunnel through the barrier and that there will be no voltage across the junction till the current reaches a critical value. Above the critical value a voltage appears and the junction oscillates at a frequency determined by the voltage. He shared the Nobel Prize in Physics (1973) with Ivar Giaever and Leo Esaki who did pioneering and technologically important work on electron tunneling in semiconductor devices. Tunneling is one of the bizarre predictions of quantum mechanics. Quantum mechanics insists that only the probability of observing an object at a particular location can be theoretically calculated and compared with experiment. How the particle arrived at that point is not merely unknown in practice but unknowable in principle. This was at the heart of the famous "philosophical" arguments between Neils Bohr and Albert Einstein. Einstein to the end of his days tried to develop an alternative physics without this limitation and failed. Later work, particularly the experiments of Alain Aspect, John Clauser and Anton Zeilinger (Nobel Prize in Physics 2022) have conclusively proved that such a theory will never be in agreement with experimental results. When an object is placed inside a cylinder with extremely thin walls, quantum mechanics predicts that there is a finite probability for the particle to be detected outside the cylinder even when it does not have the energy to climb over the walls of the cylinder. This is tunneling. See picture below. According to quantum mechanics, the energy of the particle in the cylinder in the cylinder with the thin walls can only be one of a few discrete values. If the particle is in one of the higher energy levels, the probability of tunneling will be higher.




Emission of alpha particles (Atoms of helium stripped of electrons) is the first phenomenon to be explained by tunneling, (George Gamov in 1928). Electrons and alpha particles are microscopic objects. But the Josephson effect can only be observed because a macroscopic quantum entity tunnels through the insulator. The quest of Clarke, Devoret and Martinis was to provide conclusive experimental evidence that macroscopic tunneling has taken place.

The two superconductors together with the Josephson junction are represented by a single wave function. When the current through the junction is smaller than the critical value the voltage across the junction is zero. This is one state of the quantum system. The current through the junction being larger than the critical value and the voltage across the junction being non-zero is another state of the quantum system. There is an energy barrier between the two. The system can go from the zero voltage state to the non-zero voltage state by either thermal excitation over the energy barrier or by quantum mechanical tunneling through the barrier. The rate of this transition can be experimentally determined. Thermal excitation would be temperature dependent while tunneling would be independent of changes in the temperature. But temperature independent excitation rate cannot conclusively prove tunneling because the temperature independence could be due to non thermal or excess noise.




Clarke, Devoret and Martinis relied on a theoretical analysis of the circuit developed earlier. This treats the Josephson junction with a non zero voltage across it as a resistance representing all the dissipation in the circuit and a capacitance in parallel. See picture above. This is a standard electrical circuit assumption. For a Josephson junction, the superconducting current is proportional to the sine of the phase difference. Since the voltage is time dependent, one can include the contribution of the current through the capacitance. The resulting equation is mathematically identical to the Newtonian equation of motion in the presence of an acceleration. From this one can calculate the potential which resembles a washboard. The numerous dimples are local metastable minima where the system will stay when the voltage across the junction is zero because the angle of the washboard is below a critical value. When there is a voltage, the washboard is tilted at a larger angle and the system rolls down the washboard. The visualization is complete. A classical system with the un-tilted washboard will stay indefinitely in the local metastable minimum but a quantum system may tunnel out and roll down to a state with the voltage. Also a quantum system in a higher energy state in potential minimum will have a higher probability of tunneling into a state with the voltage. The advantage of this approach is that the rates of tunneling can be theoretically calculated from parameters determined by independent experiments and compared with measurements of the time taken for the voltage to be detected spontaneously.

The laureates designed the experiment in line with this line of argument. In their setup, they used a carefully designed filter chain, with over 200 dB damping over the frequency range 0.1 to 12 GHz, using newly developed copper powder microwave filters. The thermal anchoring of the filter chain at the different temperature stages of the cryostat is important, given that black body radiation from the filters themselves is emitted at the temperature of the filters. Another very important part of the setup was a weakly coupled microwave control line for resonant activation of the junction. Resonant activation allowed for in situ determination of the junction’s plasma frequency, i.e. the resonant frequency of the particle in the local minimum in the fully classical regime. The width of the activated

resonance also allowed for characterization of the damping resistance. The junction's critical current could be determined without microwave activation. Thus, all input parameters of the theory could be independently determined. The researchers then measured escape rates below the crossover temperature in the expected regime of macroscopic quantum tunnelling. They could finally obtain quantitative agreement with theory. Irradiating the junction with 2 GHz microwaves and varying the bias current to change the potential they observed tunnelling out of the first, second and third excited state, which could be compared quantitatively with quantum mechanical calculations. The experiments performed by Clarke, Devoret and Martinis more than forty years have been accepted as indisputable confirmation of macroscopic quantum mechanical tunneling because of this close agreement between theoretical calculation and experimental observations.

Despite the elegant design of experiments and the conclusive results, award of the Nobel prize to an experiment performed more than forty years ago is slightly underwhelming. Some of the experimental methodology employed in the performance of these experiments have been used by other researchers working in quantum computing. But in addition to superconducting circuits, trapped ions, semiconductor/silicon qubits, photonic networks etc are all being investigated for use in quantum computers. So justifying the award for this experiment as a precursor to future quantum computers is perhaps misleading. Even the confirmation of macroscopic quantum mechanical tunneling should not be a great surprise to anyone. Quantum mechanics as mentioned above is counter intuitive and if one wants a macroscopic object that obeys quantum mechanics one has only to look at a neutron star. For that matter we have cosmic background radiation which shows that the universe is a perfect black body and quantum mechanics started with Max Planck proving that assuming quanta was the only way you derive the formula for black body radiation. It looks like quite a large segment of physicists do not appreciate the strength of Eugene Wigner's quote "The miracle of the appropriateness of the language of mathematics for the formulation of the laws of physics is a wonderful gift which we neither understand nor deserve". We have ample evidence that the mathematics of quantum mechanics is applicable to nature. Despite the inability of physicists to come up with a quantum theory of gravity, every other phenomenon is explicable only on the basis of quantum mechanics. So why be surprised at experiments that confirm that macroscopic quantum objects do exhibit macroscopic quantum mechanical tunneling?

To be sure while science itself may be objective, selecting a work for recognition and reward is not. Omissions and commissions can always be identified. Over the past twenty years while making these presentations I have commented occasionally on such issues. Nevertheless, my usual conclusion that Scientific understanding creates happiness even in absence of creativity stands. One can excuse one's own lack of personal contribution by noting that the creator needs an appreciative audience and hopefully the present attempt does succeed in creating in the audience an appreciation of the Nobel Prizes in Science for 2025.